Organic Syntheses

Discussion Addendum for:

Preparation of 1,1-Difluoroallenes by Difluorovinylidenation of Carbonyl Compounds

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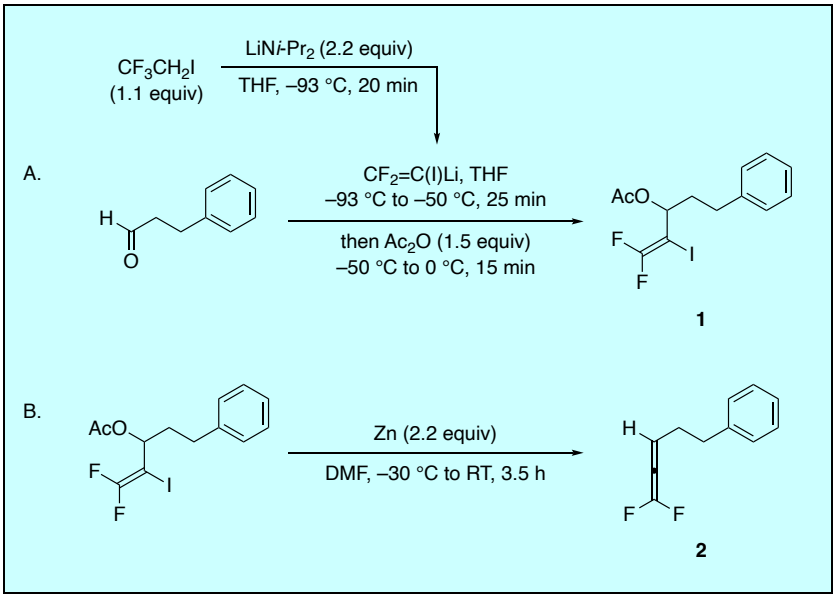
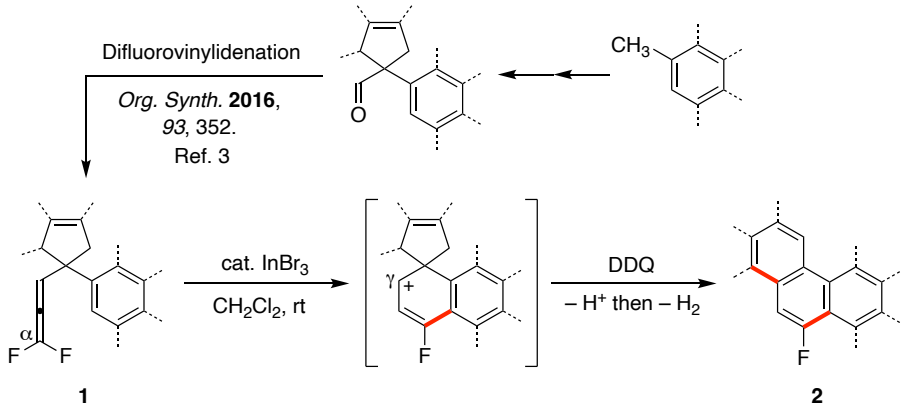


1,1-Difluoroallenes have two fluorine substituents, which are located on the cumulated diene substructure to decisively affect their reactivities. In addition to the reactions compiled in our previous review,[2] synthetic reactions of 1,1-difluoroallenes have been continuously investigated since the authors' publication in *Org. Synth.* that described difluoroallene production by difluorovinylidenation of aldehydes and ketones.[3] As a result, the fluorine

substituents allow bond-forming reactions of 1,1-difluoroallenes to proceed in α-, β-, or γ-selective fashions, all of which are illustrated below.

Bond Forming Reactions on the α-Carbon

As discussed in the original article,[3] an In(III) catalyst facilitates the domino Friedel–Crafts-type cyclization/ring expansion sequence of 1,1-difluoroallenes **1**. Subsequent one-pot dehydrogenation leads to pinpoint-fluorinated polycyclic aromatic hydrocarbons **2** (F-PAHs, Scheme 1).[4] The domino reaction allows two carbon–carbon bond formations, first at the position α to the fluorine substituents and subsequently at the γ-position.



Scheme 1. In(III)-catalyzed synthesis of F-PAHs

Three applications were developed using the above domino reaction to construct extended π systems, namely, (i) tandem benzene ring construction,[5] (ii) π-extended aryne generation,[6] and (iii) benzene ring extension.[7] These applications resulted in the successful generation of difluorinated, monofluorinated, and fluorine-free π-extended molecular systems.

The first application of the domino cyclization/ring expansion sequence involves tandem benzene ring construction (Figure 1).[5] Bis(1,1-difluoroallene) **3** (a) and **4** (b), prepared from *m*- and *p*-xylenes via the corresponding dialdehydes, underwent the domino reaction in a tandem fashion to afford pinpoint-difluorinated dibenzoanthracene **5** and picene **6** in 76% and 75% yields, respectively. The physicochemical features of the

synthesized F-PAHs were examined, specifically their solubility in organic solvents[8] and their potential as materials for electronic devices.[5]

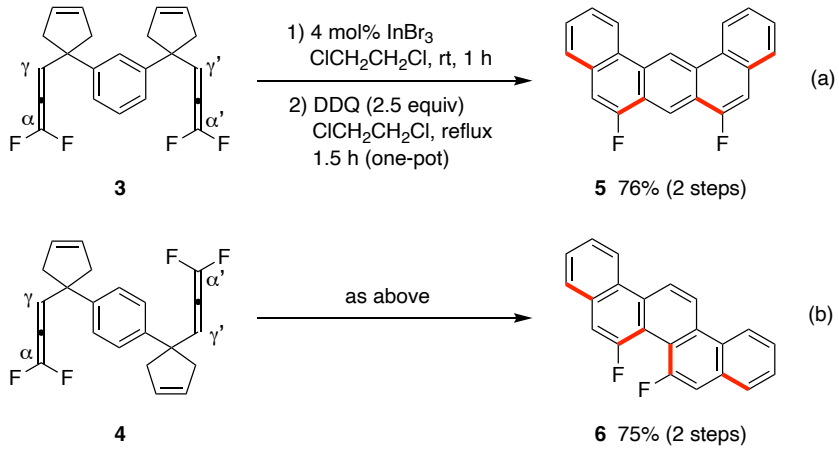
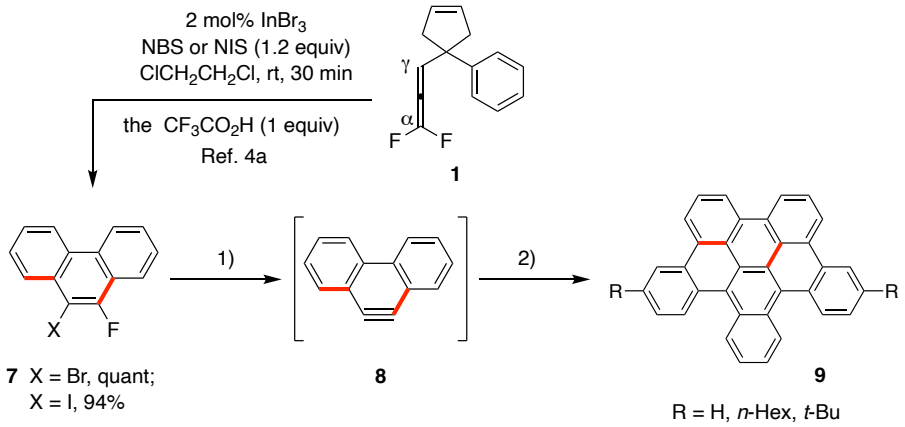


Figure 1. Synthesis of pinpoint-difluorinated PAHs (F-PAHs)

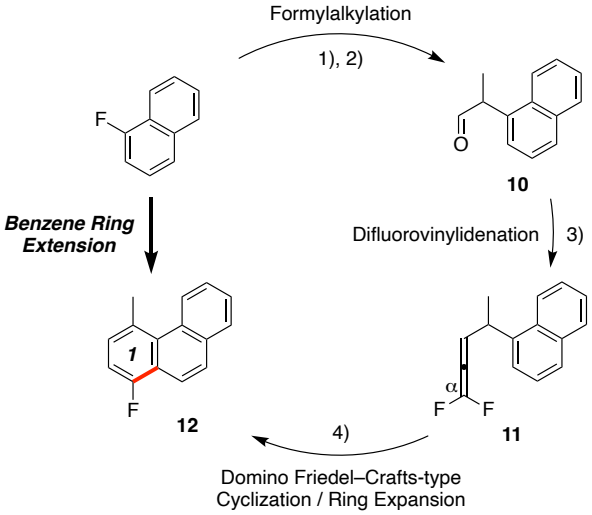
Secondly, the synthesis of "half HBCs" was facilitated by π-extended aryne generation from 1,1-difluoroallenes (Scheme 2).[6] The structure of half HBCs is a half section of HBCs (hexabenzocoronenes), which are promising as materials for photovoltaic cells. *o*-Bromo- or *o*-iodofluoroarenes **7** were prepared by the In(III)-catalyzed domino reaction of 1,1-difluoroallenes involving halogenation of the C–In bond with *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS).[4a] Compounds **7** served as precursors for π-extended arynes **8** upon treatment with butyllithium, while 6-fluoro[4]helicene (not shown) also served as an aryne precursor via dehydrofluorination upon treatment with Me_2(TMP)ZnLi (TMP, tetramethylpiperidino).[9] The produced arynes were subjected to the Diels–Alder reaction with diarylated isobenzofurans,[10] yielding cycloadducts (81–89% yields, not shown), which were easily transformed to half HBCs **9** by deoxygenative aromatization followed by aryl–aryl coupling in 78–96% yields (2 steps).



1) *n*-BuLi (1.2 equiv), diarylated isobenzofuran, Et_2O–THF (4:1), rt, 2 h (X = Br), 81–89%
2) $SnCl_2$, HBr, THF, 60 °C, 5 h to overnight then $FeCl_3$ (30 equiv), $ClCH_2CH_2Cl/MeNO_2$ (5:1) 0 °C, 0.5 to 1 h, 78–96%

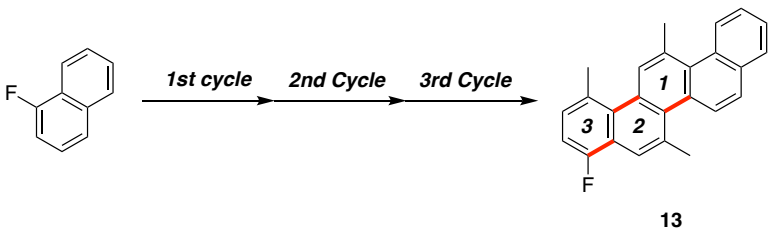
Scheme 2. Synthesis of half HBCs

Third, benzene ring extension was accomplished through the attachment of a fluorobenzo moiety to existing fluoroarenes.[7] Under microwave (MW) irradiation, commercially available 1-fluoronaphthalene was effectively cyanoethylated by aromatic nucleophilic substitution for fluorine (Figure 2). The half reduction of the nitrile gave aldehyde **10**, whose difluorovinylidenation afforded the corresponding 1,1-difluoroallene **11**. Next, **11** underwent Friedel–Crafts-type cyclization followed by dehydrofluorination to provide the benzene ring-extended fluorophenanthrene **12** in 94% yield (the first cycle). Application of second and third cycles similarly extended the π system until it eventually afforded pinpoint-fluorinated [5]phenacene (picene) **13** (Scheme 3). In addition to phenacenes with zig-zag benzene rings, such as **13**, triphenylene **14** with a trigonal structure was produced by applying the benzene ring extension cycle to internally fluorinated arenes (Scheme 4).

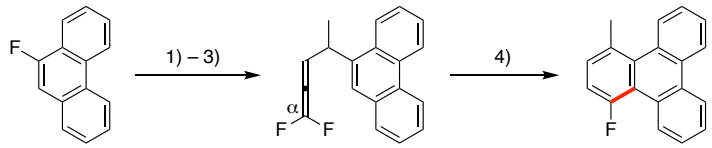


1) CH_3CH_2CN (4 equiv), KHMDS (4 equiv), THF, 80 °C
MW, 1.5 h, 82%
2) DIBAL (1.2 equiv), Toluene, –78 °C, 2 h, 81%
3) A. CF_2=C(I)Li (1.2 equiv) THF, –95 °C then Ac_2O (1.5 equiv);
B. Zn (2.0 equiv), DMF, rt, 2 h 73% (2 steps)
4) 2 mol% $InBr_3$, $ClCH_2CH_2Cl$, rt, 1 h, 94%

Figure 2. Benzene ring extension cycle



Scheme 3. Synthesis of fluorinated phenacenes

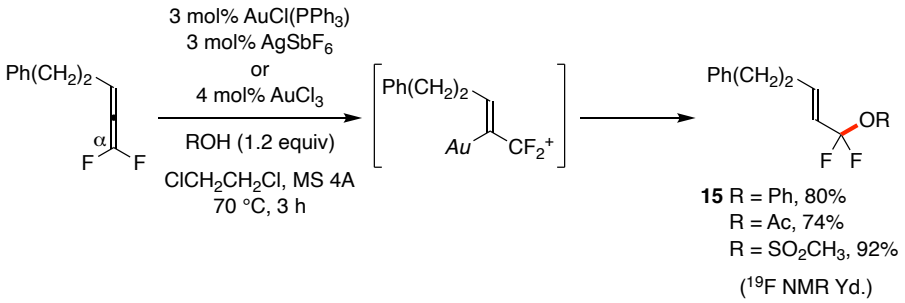


14

1) CH_3CH_2CN (4 equiv), KHMDS (4 equiv), THF, 80 °C, MW, 76%
2) DIBAL (1.2 equiv), toluene, –78 °C, 80 °C
3) A. CF_2=C(I)Li (1.2 equiv), THF, –95 °C then Ac_2O (1.5 equiv);
B. Zn (2.0 equiv), DMF, rt, 61% (2 steps)
4) 2 mol% $InBr_3$, $ClCH_2CH_2Cl$, rt, 98%

Scheme 4. Synthesis of fluorinated triphenylenes

Apart from cyclizations, 1,1-difluoroallenes also undergo α-selective addition of oxygen nucleophiles, such as phenols, carboxylic acids, and sulfonic acids, in the presence of an Au(I) or an Au(III) catalyst (Scheme 5).[11] Thus, using the aurated allylic CF_2 cations, the hard O-nucleophiles were regioselectively introduced to 1,1-difluoroallenes, yielding 1,1-difluoroallylic ethers and esters **15** in 74%–92% yields. In contrast, soft sulfur and nitrogen nucleophiles underwent γ-selective addition (vide infra: Scheme 9).



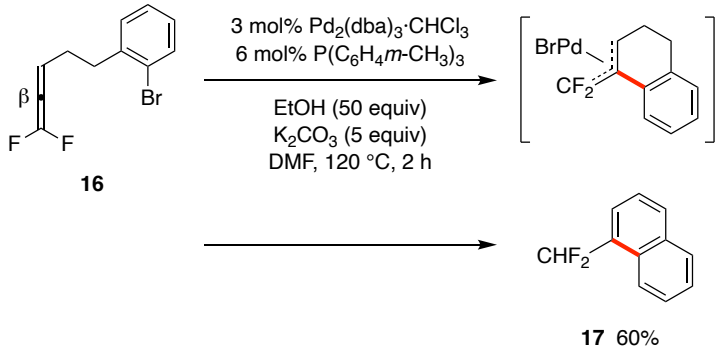
15 R = Ph, 80%
R = Ac, 74%
R = SO_2CH_3, 92%
(^{19}F NMR Yd.)

Scheme 5. Synthesis of 1,1-difluoroallylic ethers and esters

Bond Forming Reactions on the β-Carbon

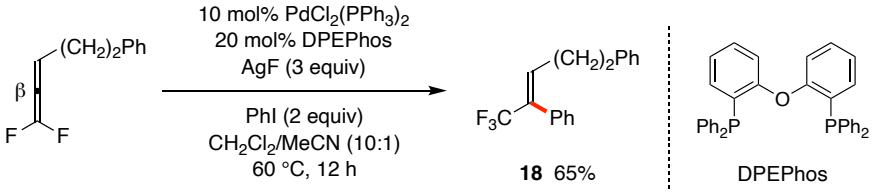
Bond-forming reactions at the position β to the fluorine substituents were facilitated by a palladium catalyst involving π-allylpalladium(II) formation.[12] Difluoroallene **16** with a bromophenyl moiety was intramolecularly carbopalladated to form the π-allylpalladium(II) species with a six-membered ring structure, which in turn underwent β-hydrogen elimination,

followed by isomerization to yield difluoromethylated naphthalene **17** in 60% yield (Scheme 6). The difluoromethyl group is a bioisostere of a hydroxy group and is attracting attention in the field of pharmaceuticals and agrochemicals as a hydrogen donor for hydrogen bonding while simultaneously exhibiting hydrophobicity.

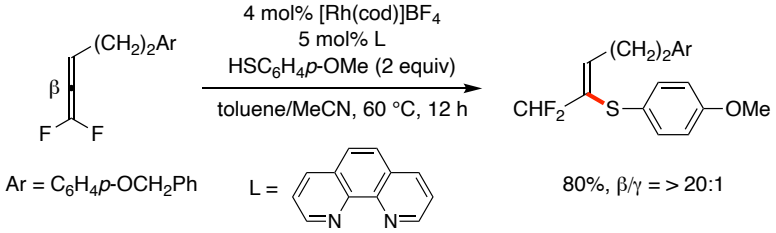


Scheme 6. Synthesis of difluoromethylated naphthalenes

The intramolecular β-selective carbometallation was followed by intermolecular fluorometallation (cat. Pd(0)/PhI/AgF, Scheme 7),[13] where the generation of vinylsilver(I) was proposed to participate in Pd(0)-catalyzed coupling, leading to (trifluoromethyl)alkene **18** in 65% yield. A rhodium(I) catalyst bearing a nitrogen ligand facilitated C–S bond formation in a β-selective fashion (Scheme 8), while Rh(I) with a phosphine ligand promoted γ-addition (vide infra: Scheme 10).[14]



Scheme 7. Synthesis of arylated (trifluoromethyl)alkenes



Scheme 8. Synthesis of sulfanylated (difluoromethyl)alkenes

Bond Forming Reactions on the γ-Carbon

Organocopper(I) reagents promote γ-selective bond-forming reactions in almost all cases.[15] 3-Monosubstituted 1,1-difluoroallene **19** reacted with ethylcopper(I) to afford the corresponding addition product, γ-branched 1,1-difluoro-1-alkene **20** (E = H), in 95% yield via protonolysis of the 2,2-difluorovinylcopper(I) intermediate (Figure 3).[16] When quenched by electrophiles, such as halogenating agents and halostannanes, β-functionalized 1,1-difluoro-1-alkenes **21** and **22**, respectively (66%–84% yields). The 2,2-difluorovinylcopper(I) intermediates enabled Pd(0)-catalyzed coupling with iodobenzene, yielding a three-component coupling product **23** in 90% yield.

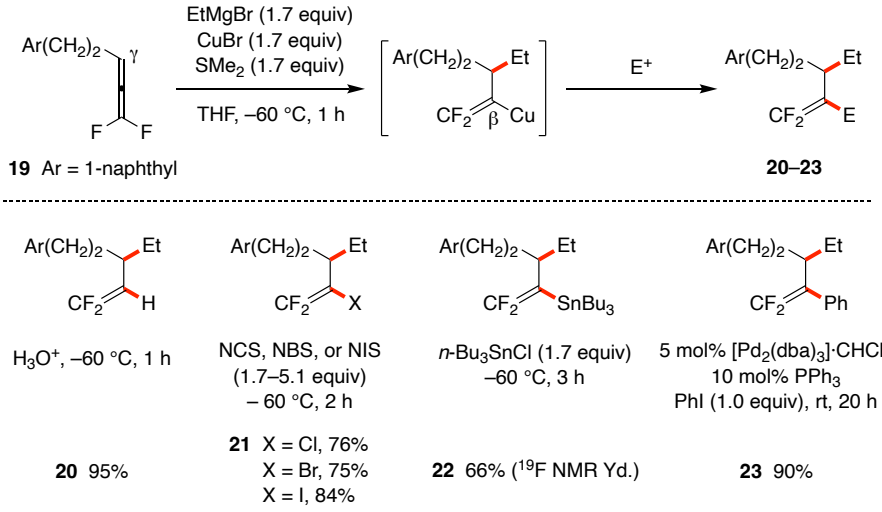


Figure 3. Synthesis of γ-branched 1,1-difluoro-1-alkenes

B_2pin_2 and $PhMe_2SiBpin$ with a Cu(I)-catalyst promoted γ-selective borylation and silylation of 1,1-difluoroallenes, which afforded 3,3-difluoroallylboronate **24** and silane **25** in 86% yields, respectively (Figure 4).[17] The formed difluoroallylboronates reacted with aldehydes to provide 2,2-difluorohomoallylic alcohols (not shown).

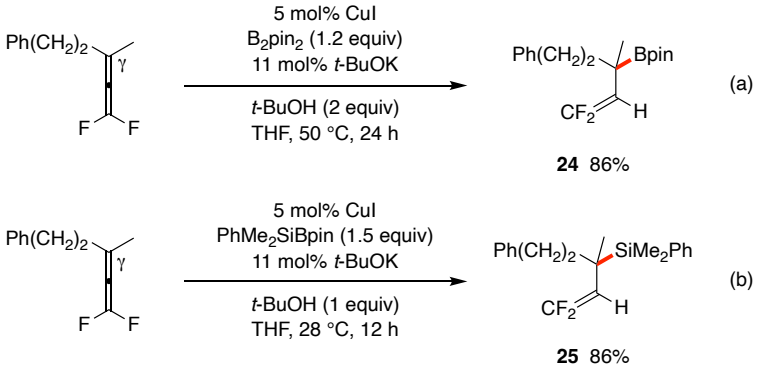
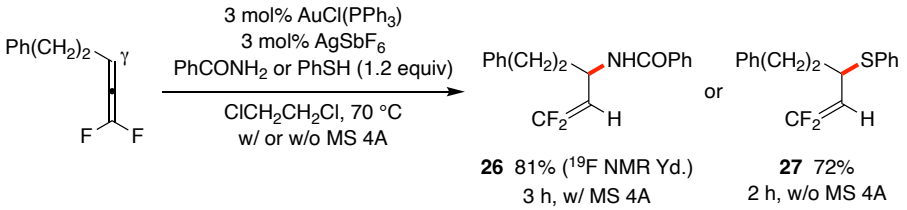
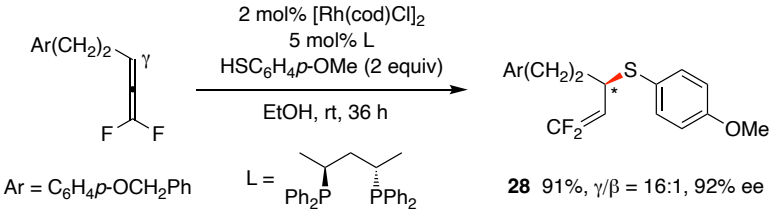


Figure 4. Synthesis of 3,3-difluoroallylic boronates and silanes

As well as undergoing alkylation, borylation, and silylation reactions, 1,1-difluoroallenes underwent the γ-selective addition of benzamide and thiophenol in the presence of an Au(I) [or an Au(III)] catalyst through cationic intermediates (Scheme 9, see also: Scheme 5).[11] 3,3-Difluoroallylic amine **26** and thioether **27** were synthesized in 81% and 72% yields, respectively. The use of a Rh(I) catalyst with a chiral phosphine ligand aided in the synthesis of chiral 3,3-difluoroallylic thioether **28** via γ-selective C–S bond formation (Scheme 10, see also: Scheme 8).[14]

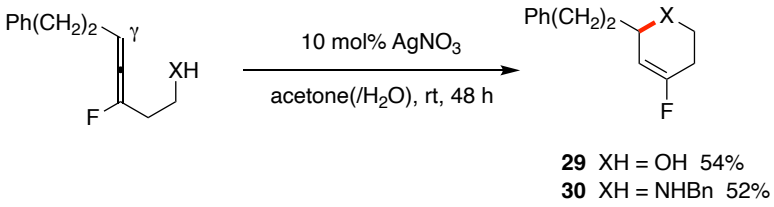


Scheme 9. Synthesis of 3,3-difluoroallylic amines and thioethers



Scheme 10. Synthesis of chiral 3,3-difluoroallylic thioethers

The related monofluoroallenes underwent γ-selective intramolecular C–O and C–N bond formations in the presence of an Ag(I) catalyst (Scheme 11). Ring-fluorinated heterocycles, dihydropyran **29**, and tetrahydropyridine **30**, were obtained in 54% and 52% yields, respectively.[18]



Scheme 11. Synthesis of heterocyclic fluoroalkenes

In summary, since our report on the synthesis of 1,1-difluoroallenes by carbonyl difluorovinylidenation, the reactions of 1,1-difluoroallenes have been steadily investigated and their unique reactivities have been revealed. Now, regioselective bond-forming reactions in 1,1-difluoroallenes can be successfully effected at each of the three, α-, β-, and γ-positions with the aid of metals, such as In(III), Au(I), Au(III), Pd(0), Cu(I), and Ag(I), which enables the synthesis of fluorinated and fluorine-free cyclic and acyclic molecules. As a result, 1,1-difluoroallenes are extremely adaptable synthetic building blocks. Despite these advances in ionic reactions, further research on their behavior under radical conditions and in electrocyclization processes is still required.[19]

References

1. Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305–8571, Japan. E-mail: kfuchibe@chem.tsukuba.ac.jp (ORCID: 0000-0002-6759-7003); junji@chem.tsukuba.ac.jp. (ORCID: 0000-0001-6498-326X). This work was partially supported by TOSOH FINECHEM CORPORATION.
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Junji Ichikawa was born in Tokyo, Japan in 1958. He received his B.Sc. in 1981 and Ph.D. in 1986 from the University of Tokyo (Prof. T. Mukaiyama). He joined Kyushu University as an Assistant Professor in 1985. In 1989, he was a research associate at Harvard University (Prof. E. J. Corey) and then worked at Kyushu Institute of Technology as a Lecturer and an Associate Professor. In 1999, he moved to the University of Tokyo as an Associate Professor. He was appointed as a Professor at University of Tsukuba in 2007. His research interests lie in the area of synthetic methodology based on the properties of metals and fluorine.